

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re patent application of

David Reginald ADAMS et al.

Serial No. 09/890,186

Filed: 10/09/2001

For: PIRAZINO(AZA)INDOLE DERIVATIVES

Attorney Docket No. 040283-0192

Group Art Unit: 1624

Examiner: V. Balasubramanian

**DECLARATION UNDER 37 CFR § 1.132**  
**OF NATHANIEL JULIUS THOMAS MONCK**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Nathaniel Julius Thomas Monck, the undersigned, a citizen of Great Britain and a resident of Wokingham, United Kingdom, do hereby declare that:

1. I am the Senior Scientist responsible for the 5HT<sub>2C</sub> project and I am familiar with the invention described in the above-identified patent application entitled "PIRAZINO(AZA)INDOLE DERIVATIVES " which was given United States Serial No. 09/890186.

2. I graduated as a Bachelor of Science from University of Bristol in 1990, and completed a Doctoral Degree from Imperial College, London University in 1993.

3. Since August 1996, I have been employed by VERNALIS RESEARCH LIMITED, assignee of the above-identified application, where I have been engaged in research and development of drugs useful in the treatment of CNS disorders.

4. I attach my Curriculum Vitae.

5.1 It is my understanding that the Examiner considers the subject-matter claimed in the above-identified application to be obvious over Mokrosz *et al* (Med. Chem. Res. 3: 240-248, 1993).

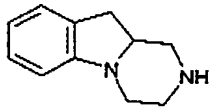
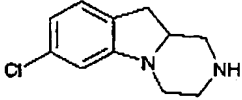
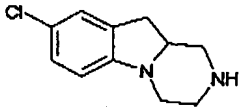
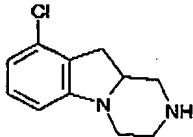
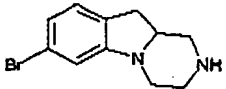
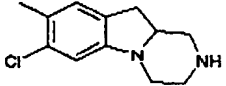
5.2 Compounds (6) and (7) in the Mokrosz prior art differ from the presently

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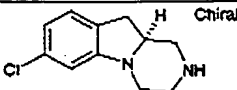
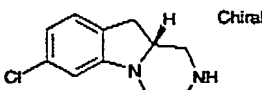
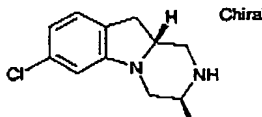
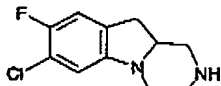
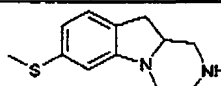
claimed compounds in that the phenyl ring is unsubstituted. The presently claimed compounds require that at least one of the R<sub>4</sub> to R<sub>7</sub> groups of the phenyl ring is not hydrogen. It is my understanding that the Examiner considers these substituted compounds to be obvious. However, we have been able to show an unexpected advantage of the presently claimed compounds.

5.3 The comparative data are set out in Tables 1 and 2 below. Table 1 shows the weak efficacy of the unsubstituted compounds of Mokrosz. In contrast, all the presently claimed substituted compounds have EC<sub>50</sub> values from 7 to 300-fold lower than the unsubstituted examples of the prior art. The presently claimed compounds therefore possess greater agonist potency than those of Mokrosz. The superiority of the presently claimed compounds could not have been predicted, and we believe therefore that the claimed subject-matter should not be considered obvious.

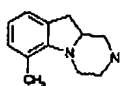
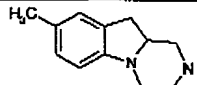
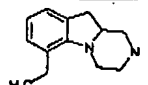
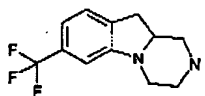
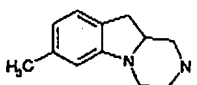
**Table 1**

Compound	Structure	EC <sub>50</sub> (5-HT <sub>2C</sub> )
Prior Art Example		1085 nM
Example 1		18
Example 2		162
Example 3		141
Example 4		13
Example 5		20

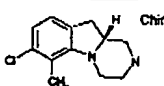
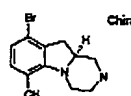

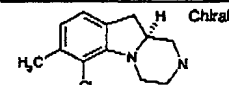
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Example 7		161
Example 8		3
Example 11		58
Example 12		22
Example 13		86

**Table 2**

Structure	R group exemplified	EC50 5HT2C / nM
	R4 = methyl	129
	R6 = methyl	43
	R4 = ethyl	47
	R5 = trifluoromethyl	102
	R5 = methyl	29

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	R4 = methyl R5 = chloro	116
	R4 = methyl, R7 = bromo	24
	R4 = trifluoromethoxy	57
	R4 = chloro, R5 = methyl	44

6. I further declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date:

16<sup>th</sup> January 2004  
Nathaniel Julius Thomas Monck

**Nathaniel Julius Thomas Monck**

10 Park Crescent, Sunningdale, Berkshire, SL5 0AX, UK.

Date of Birth: 16 July 1968

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**Professional Experience:**

- Aug 1996-present date      **Vernalis Research Ltd**, Winnersh Triangle.  
Principal Scientist, Chemistry Dept.  
Anxiety Project Leader (chemistry) 1997-2001  
Sodium Channel Project Leader (chemistry) 2001-present date
- Feb 1996-Aug 1996      **SmithKline Beecham**, Harlow.  
Industrial post-doctoral position.  
Synthesis of conformationally restricted unnatural amino-acids and incorporation into peptide mimetic libraries via combinatorial chemistry.
- Feb 1995-Nov 1995      **The Australian National University**, Canberra, ACT.  
Post-Doctoral Research Fellow  
Research Advisor: Professor Lewis N. Mander, FRS  
Studies towards the total synthesis of gibberellic acid GA<sub>103</sub>, the total synthesis of Harringtonolide and the partial synthesis of 7 $\beta$ -hydroxy-kaur-16-en-19-oic acid.
- Jan 1994-Jan 1995      **The Ohio State University**, Columbus, Ohio.  
Post-Doctoral Research Fellow  
Research Advisor: Professor Leo A. Paquette  
Studies towards the total synthesis of Jatrophatrione.
- Oct 1990-Dec 1993      **Imperial College**, University of London.  
Research Fellow; Research Advisor: Professor Steven V. Ley, FRS  
Development of new synthetic methods for the total synthesis of Milbemycin  $\alpha_1$  and Nemadectin  $\beta$  utilising relay studies of Nemadectin  $\gamma$ .  
Undergraduate Teaching Assistant; supervision and demonstration of laboratory experiments.
- Oct 1992-Dec 1992      **Rhône-Poulenc-Rorer**, Dagenham.  
Research Fellow; Research Advisor: Dr Michael Ashton  
CASE award industrial placement.
- Jul 1989-Aug 1989      **Institute of Child Health/Great Ormond Street Hospital**, London.  
Research Assistant; Research Advisor: P. Bird.  
Studies towards the development of HPLC methods for the analysis of samples from neofibroblastomer patients.

### Awards/Honours:

- 1997-1998 MRSC CChem awarded as result of Structured Assessment.  
1990-1993 CASE Award from Rhône-Poulenc-Rorer.

### Courses:

- Dec 1998 Introduction to Molecular Modelling, including the use of Legion, Selector, Flexidock and Gasp operations; Tripos Inc., Milton Keynes  
July 1997 Medicinal Chemistry Residential Course: An introduction to the pharmaceutical industry. RSC, Canterbury.

### Education:

- 1990-1993 Imperial College, University of London  
PhD, DIC, Synthetic Organic Chemistry  
Research Advisor: Professor Steven V. Ley, FRS  
Dissertation: Studies towards the Total Synthesis of the Milbemycins.  
1987-1990 University of Bristol,  
Bachelor of Science (Hons), Chemistry, First class.  
Final year project supervisor: Dr Thomas V. Lee  
Dissertation: The Use of Enzymes in Organic Media.  
1979-1986 Acland Burghley Comprehensive School, London  
A-levels: Chemistry (A), Mathematics (B), Physics (A)  
O-levels: French, History, Geography, Music, Chemistry, Physics, Mathematics, Advanced Mathematics, English Literature, English Language.

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**Preparation of azetidine carboxamides for the treatment of CNS disorders.** Snape, Mike Frederick; Fletcher, Allan; Stanhope, Kelly Jean; Monck, Nathaniel Julius. (Vernalis Research Limited, UK). PCT Int. Appl. (2001), 39 pp. CODEN: PIXXD2 WO 0107043 A1 20010201.

**Preparation of azetidine-1-carboxamide derivatives as neuroprotectants.** Snape, Mike; Monck, Nathaniel Julius; Fletcher, Allan; Stanhope, Kelly Jean; Mansell, Howard Langham; Nelson, Alan John. (Vernalis Research Limited, UK). PCT Int. Appl. (2001), 31 pp. CODEN: PIXXD2 WO 0107023 A2 20010201.

**2-adamantanemethanamine compounds for treating abnormalities in glutamatergic neurotransmission, and preparation thereof.** Gillespie, Roger John; Monck, Nathaniel Julius Thomas; Bird, Andrew James; Ward, Simon Edward. (Vernalis Research Limited, UK). PCT Int. Appl.

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**3,5-Disubstituted-4-hydroxyphenyls Linked to 3-Hydroxy-2-methyl-4(1H)-pyridinone: Potent Inhibitors of Lipid Peroxidation and Cell Toxicity.** Bebbington, David; Monck, Nathaniel J. T.; Gaur, Suneel; Palmer, Alan M.; Benwell, Karen; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Departments of Chemistry and Molecular Pharmacology, Cerebrus, Wokingham, UK. *Journal of Medicinal Chemistry* (2000), 43(15), 2779-2782.

**Dual-mechanism antioxidants: Novel neuroprotective compounds--II.** Bebbington, David; Gaur, Suneel; Dawson, Claire E.; Monck, Nathaniel J. T.; Palmer, Alan M.; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Department of Chemistry, Cerebrus, Wokingham, UK. Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-093.

**Synergistic dual-mechanism antioxidants: Novel neuroprotective compounds--I.** Bebbington, David; Monck, Nathaniel J. T.; Gaur, Suneel; Palmer, Alan M.; Benwell, Karen R.; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Department of Chemistry, Cerebrus, Wokingham, UK. Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-092.

**Preparation of indolinealkylamine derivatives as 5-HT<sub>2B</sub> and/or 5-HT<sub>2C</sub> receptor ligands.** Adams, David Reginald; Bentley, Jonathan Mark; Roffey, Jonathan Richard Anthony; Hamlyn, Richard John; Gaur, Suneel; Duncton, Matthew Alexander James; Bebbington, David; Monck, Nathaniel Julius; Dawson, Claire Elizabeth; Pratt, Robert Mark; George, Ashley Roger. (Cerebrus Pharmaceuticals Limited, UK; et al.). *PCT Int. Appl.* (2000), 81 pp. CODEN: PIXXD2 WO 0012475 A1 20000309.

**Preparation of 2-adamantanecarboximidamides NMDA receptor antagonists.** Monck, Nathaniel Julius Thomas; Gillespie, Roger John; Bird, Andrew James. (Cerebrus Limited, UK). *PCT Int. Appl.* (1999), 34 pp. CODEN: PIXXD2 WO 9938841 A1 19990805.

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**Preparation of ortho-hydroxypyridinone derivatives as iron chelating and antioxidant agents.** Bebbington, David; Monck, Nat; Gaur, Suneel; Palmer, Alan; Porter, Richard; Malcolm, Craig. (Cerebrus Limited, UK). *PCT Int. Appl.* (1999), 68 pp. CODEN: PIXXD2 WO 9923075 A1 19990514.

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Nathaniel J. T.; Morris, Jonathan C.; Zhang, Hongbin; Mander, Lewis N. Research School of Chemistry, Inst. of Advanced Studies, Australian National Univ., Canberra, Australia. Pure Appl. Chem. (1998), 70(2), 351-354.

**A New and Efficient Strategy for the Total Synthesis of Polycyclic Diterpenoids: The Preparation of Gibberellins ( $\pm$ )-GA103 and ( $\pm$ )-GA73.** King, Geoffrey R.; Mander, Lewis N.; Monck, Nathaniel J. T.; Morris, Jonathan C.; Zhang, Hongbin. Research School of Chemistry, Australian National University, Canberra, Australia. J. Am. Chem. Soc. (1997), 119(16), 3828-3829.

**Total synthesis of the spiroketal macrolide (+)-milbemycin  $\alpha$ 1.** Ley, Steven V.; Madin, Andrew; Monck, Nathaniel J. T.. Univ. Chem. Lab., Cambridge, UK. Tetrahedron Lett. (1993), 34(46), 7479-82.